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Summary

Within this study medicinal plants traditionally used against urinary tract infections were screened on a potential antiadhesive activity against uropathogenic *Escherichia coli* (UPEC). Systematic review of the literature revealed the presence of 242 plants described for this use. Based on certain assessment criterions a shortlist of 20 herbs was established for detailed *in vitro* investigation. EtOH:water extracts of these plants were examined in an *in vitro* adhesion assay against UPEC, using different experimental setups in order to distinguish between an influence of the extracts on bacteria (A2980) or on human bladder cells (T24 cells). The experiments revealed significant dose-dependent antiadhesive activity for extracts prepared from *Maydis stigmata* (*Zea mays* L., IC_{50} 1040 µg/mL) and *Graminis rhizoma* (*Agropyron repens* L., IC_{25} 630 µg/mL) by an influence on bacterial adhesins. Furthermore extracts from *Betulae folium* (*Betula* spp., IC_{50} 415 µg/mL), *Orthosiphonis folium* (*Orthosiphon* spp., IC_{50} 1330 µg/mL), and *Urticae folium* (*Urtica* spp., IC_{25} 588 µg/mL) were demonstrated to inhibit the adhesion significantly in a dose-dependent manner by an interaction with T24 bladder cells. A further experimental setup was used with the aim to investigate potential synergistic effects by testing combinations of extracts with activity on bacteria on the one hand and on T24 cells on the other hand. This approach revealed that a combination of *Maydis stigmata* or *Graminis rhizoma* with *Orthosiphonis folium* decreased significantly the bacterial adhesion compared to values observed for each individual extract.

Bioassay-guided fractionation of *Maydis stigmata* extract by column chromatography on Sephadex® LH-20 as stationary phase led to the isolation of two subfractions (I and XI) with strong antiadhesive activity against UPEC. Structural elucidation of a bioactive compound isolated from fraction I revealed benzethonium chloride, a synthetic contaminant. The plant material of three different commercial batches of *Maydis stigmata* showed benzethonium chloride contamination of approx. 2.6 ppm. A further batch of *Maydis stigmata* obtained from a different supplier was free of benzethonium chloride: fraction I isolated from this non-contaminated plant material exhibited no activity against the bacteria. However, fraction XI of this material showed antiadhesive activity (IC_{50} 405 µg/mL). This fraction was subjected to a bioassay-

guided fractionation and subsequent LC-MS studies suggested the presence of potential antiadhesive maysin derivatives (subfraction XI_G: IC_{50} 690 µg/mL).

A commercial proanthocyanidin enriched cranberry (*Vaccinium macrocarpon* AIT.) extract (named *V.m. extract*) as well as a tannin free preparation of this extract (named *V.m. extract*$^{\neq PAC}$) were investigated within various functional test systems against two different UPEC strains (A2980 and NU14). Both strains were characterized concerning their respective virulence factor expression profiles by differential gene expression analysis. The adhesion assay revealed results which were dependent on adhesins expressed by each respective strain. *V.m. extract* evoked in both strains an increase of bacterial adhesion due to agglomeration of bacteria, whereby a significant difference in the intensity of enhanced adhesion was determined between the strains. In contrast, adhesion assay using *V.m. extract*$^{\neq PAC}$ resulted for A2980 in nearly unchanged bacterial adhesion, comparable to that of the untreated control, while the adhesion of NU14 was significantly decreased at a concentration of 100 µg/mL (28 ± 2 %). The influence of both extracts on the expression of bacterial adhesins was investigated by differential gene expression analysis revealing results which were in accordance to the outcome of the adhesion assay. Adhesion of UPEC strain A2980 to bladder cells was strongly increased as tannins of *V.m. extract* led to agglomeration of bacteria and induced in addition an approx. two fold upregulation of the expression of the adhesins PapGII and FocG, possibly as a reaction to binding of PapGII by PACs. These adhesins are not expressed by UPEC strain NU14. Treatment of UPEC strain A2980 with *V.m. extract*$^{\neq PAC}$ did not change the expression rate of adhesins. Decreased adhesion of UPEC strain NU14 to T24 cells after incubation of bacteria with *V.m. extract*$^{\neq PAC}$ was presumably due to an influence of the extract on the adhesin FimH (not expressed by A2980) which was approx. two fold upregulated probably as part of a feedback mechanism. Biofilm assay revealed that both extracts had no influence on biofilm formation of the UPEC strains A2980 and NU14. Furthermore, it was observed that both extracts did not interact with the formation of curli on the surface of UPEC strain NU14. For the strain A2980 it was additionally demonstrated that bacteria after incubation with *V.m. extract* are significantly inhibited in their ability to invade into the bladder cells.

Within an *in vivo*/*ex vivo* pilot study with four human male volunteers, treated for seven days with 600 mg (per day) extract from *Vaccinium macrocarpon* AIT., it was shown that urine collected after cranberry intake exhibited significant antiadhesive effects up to 50 % against UPEC strain NU14.